Complete Summary

GUIDELINE TITLE

2002 national guideline for the management of anogenital warts.

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of anogenital warts. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [43 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Anogenital warts

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To present a national guideline on the management of anogenital warts

TARGET POPULATION

Patients in the United Kingdom with anogenital warts

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

1. Assessment of clinical features of lesions
    - Naked eye examination
    - Females, vaginal speculum
    - Both sexes, proctoscopy
    - Meatoscopy, urethroscopy as indicated
    - Recording lesions on genital maps
    - Extragenital site examination
2. Classification of warts as to morphology
3. Biopsy under local anaesthetic for histology, plus or minus colposcopy

Management/Treatment

1. General advise and patient education
2. Further investigations
    - Evaluation for concurrent sexually transmitted infections
    - Investigation of subclinical lesions
3. Pharmacotherapy/chemical applications
    - Podophyllin and Podophyllotoxin
    - Trichloroacetic acid
    - Imiquimod
    - Interferon: intralesional; systemic; topical
    - 5-Fluorouracil
4. Ablation therapy
    - Cryotherapy
    - Surgical/scissor excision
    - Electrocautery/electrotherapy
    - Laser therapy: carbon dioxide laser
    - Loop electrode excision procedure
5. No treatment
6. Assessment of current sexual partner
7. Follow-up
8. Special considerations for the following anatomical sites: intravaginal, cervix, urethral meatus, intra-anal
9. Special considerations for pregnant women
10. Cervical cytology screening intervals

MAJOR OUTCOMES CONSIDERED

- Clearance and recurrence rates of anogenital warts
- Adverse effects of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

OVID/Medline was searched for the years 1966-2000 using keywords "human papillomavirus", "genital warts", "epidemiology", "clinical manifestations", "treatment", "management", "laryngeal papillomatosis".

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The revision process commenced with authors being invited to modify and update their 1999 guidelines. These revised versions were posted on the website for a 3 month period and comments invited. The Clinical Effectiveness Group and the authors concerned considered all suggestions and agreed on any modifications to be made.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial versions of the guidelines were sent for review to the following:

- Clinical Effectiveness Group (CEG) members
- Chairs of UK Regional GU Medicine Audit Committees who had responded to an invitation to comment on them
- Chair of the Genitourinary Nurses Association (GUNA)
- President of the Society of Health Advisers in Sexually Transmitted Diseases (SHASTD)
- Clinical Effectiveness Committee of the Faculty of Family Planning and Reproductive Health Care (FFP).

Comments were relayed to the authors and attempts made to reach a consensus on points of contention with ultimate editorial control resting with the Clinical Effectiveness Group. Finally, all the guidelines were ratified by the councils of the two parent societies.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (I-IV) and grades of recommendation (A-C) are repeated at the end of the "Major Recommendations" field.

Diagnosis

- Naked eye examination in most cases
- If in doubt, or lesion is atypical or pigmented, biopsy under local anaesthetic for histology should be performed prior to any therapeutic intervention. This may be aided by the use of a colposcope.

Assessment of lesions

- Examine the external anogenital and surrounding skin under good illumination
- Females, vaginal speculum
- Both sexes, proctoscopy may be indicated if history of anal receptive sex, or following clearance of perianal warts. Meatoscopy and proctoscopy should be performed if there is a history of distortion of urine flow or bleeding from the

urethra or anus. Occasionally urethroscopy is indicated for more proximal warts.
- Classify warts as to morphology
- Recording of lesions on genital maps at each visit is useful, providing a visual record of approximate number, distribution, and response to treatment
- Extragenital sites (e.g., oral cavity) examined if clinically indicated.

Management

General advice

- Patients should be given a detailed explanation of their condition with particular emphasis on the long term implications for the health of themselves and their partners. This should be reinforced by giving them clear and accurate written information.
- Condom usage with regular sex partners has not been shown to affect the treatment outcome in anogenital warts (Krebs & Helmkamp, 1991), although one study suggested a reduction in new human papilloma virus associated lesion formation (Hippelainen et al., 1994), but many patients and partners feel more comfortable using these while the warts are visible. The use of condoms may prevent transmission of human papilloma virus to uninfected partner(s) (Hippelainen et al., 1994) and should be encouraged.
- For some patients the psychological impact of warts is the worst aspect of the disease. (CDR Weekly, 2000) Where psychological distress is apparent, referral for counselling may be appropriate.

Further investigations

Many patients will have other concurrent sexually transmitted infections. Therefore, an appropriate screen for sexually transmitted infections is recommended (Pakianathan, Ross, & McMillan, 1996).

Subclinical lesions

Subclinical lesions of the external anogenital skin are those not seen by the naked eye, but detectable by soaking the skin with 5% acetic acid and examining with a colposcope. These lesions are usually asymptomatic, but may cause irritation and inflammation of the skin- for example, atypical balanoposthitis (Wikstrom et al., 1994) or vulvitis (Boden et al., 1988).

Problems associated with the identification of such lesions:

- Many aceto-white lesions are not caused by human papilloma virus (Wikstrom et al., 1992)
- Histological changes are not specific for human papilloma virus infection (Voog, 1996)
- Human papilloma virus identification is not routinely available.

Treatment of these has not been shown to:

- affect the course of disease (Riva et al., 1989)

- affect the course of disease in partners (Krebs & Helmkamp, 1991)

For the above reasons and the fact that identification may cause unnecessary distress, it is not recommended that these lesions be sought unless there is a clinical indication (level of evidence IIb, grade of recommendation B).

Treatment

- All treatments have significant failure and relapse rates.
- Treatment decisions should be made after discussing the appropriate options with the patient, taking into account their preference and convenience.
- Treatment may involve discomfort and local skin reactions. Written information on management of treatment side effects is recommended.
- Local anaesthetic cream plus or minus injection with, for example, Lignocaine 2% could be used before ablative therapy to minimize discomfort. Adrenaline-containing anaesthetic should be avoided for lesions on the penis and around the clitoris.
- Warticon and Condyline (Podophyllotoxin) hold license for treatment of genital warts but not extragenital lesions such as anal warts. They are licensed for 4 and 5 week courses respectively. It is recommended that when lesion area treated is greater than 4 cm^2 that treatment takes place under direct supervision of medical staff. 5-Fluorouracil is licensed for treatment of malignant and non-malignant skin lesions. Common practice in the treatment of anogenital warts is to use these compounds out of license. It should be noted that such use is a doctor's responsibility.

Treatment choice

- The evidence base to direct first and second line treatments is not strong.
- Treatment choice depends on the morphology, number, and distribution of warts.
- Soft non-keratinised warts respond well to podophyllin, podophyllotoxin, and trichloroacetic acid.
- Keratinised lesions are better treated with physical ablative methods such as cryotherapy, excision, or electrocautery. (Eron, 1992)
- Imiquimod may be suitable for both types.
- People with a small number of low volume warts irrespective of type are best treated with ablative therapy from the outset.
- Podophyllotoxin for 4 week cycles and imiquimod for up to 16 weeks are suitable for home treatment by patients. If chosen, the patient should be given a demonstration on lesion finding and treatment application.
- No treatment is an option at any site and may apply particularly to warts in the vaginal and anal canal.

Treatments available

Clearance and recurrence rates for individual treatments are shown in table 1 of the guideline document. (Beutner & Wiley, 1997)

Chemical applications

Podophyllin

Podophyllin is a non-standardized cytotoxic compound. It has been associated with severe local reactions. Serious systemic adverse events have occurred when used outside guidelines. (Marcus & Camisa, 1990) Podophyllin is licensed for prescription use only. Best practice described in the British National Formulary recommends supervised application in genitourinary medicine clinics or general practice by trained nurses after screening for other sexually transmitted diseases. Animal experiments indicate teratogenic and oncogenic properties (Sabine, Horton, & Wicks, 1973; Kaminetsky & Swerdlow, 1965; Joneja & Liever, 1974; Thiersch, 1963; Ferguson & Pearson, 1992) but evidence of these in humans is lacking.

- 15-25% solution can be carefully applied to lesions, in clinic, once or twice weekly. Wash off 4 hours later (Ib, A)

Caution:

- Podophyllin has caused serious systemic side effects if applied in excess. Increased systemic absorption is likely if used internally. Limit application to 10 cm^2 or 0.5 ml for external warts, and less than 2 cm^2 for vaginal warts (IV, C) (Centers for Disease Control and Prevention, 1993).
- The potential oncogenic and teratogenic effects as noted indicate it should be avoided on the cervix and in the anal canal, and in pregnancy (IV, C).

The adverse problems associated with Podophyllin and its inferior efficacy to Podophyllotoxin (Lassus et al., 1987; Edwards, Atma-Ram, & Thin, 1988; Marzukiewicz & Jablonska, 1990; Kinghorn et al., 1993) (IIaB) - greater than 20% clearance in each of the quoted studies in favour of Podophyllotoxin - have led some experts to no longer recommend the use of Podophyllin. (von Krogh et al., 2000)

Combination therapy

Applying Podophyllin in conjunction with cryotherapy is a common practice in the United Kingdom (Wardropper & Woolley, 1992) although there are no studies to validate this approach.

Podophyllotoxin

Podophyllotoxin, a purified extract of podophyllin in the form of a 0.5% solution or 0.15% cream, is suitable for home treatment (Ib, A).

- Treatment cycles consist of twice daily application for 3 days, followed by 4 days' rest for 4 cycles.
- The cream may be easier for many patients to apply, especially at the anus.
- Discontinue treatment if significant side effects.

Caution: Avoid in pregnancy.

Trichloroacetic acid

Trichloroacetic acid 80-90% solution is suitable for weekly application in a specialist clinic setting only. It acts as a caustic agent resulting in cellular necrosis (Ib, A).

- An intense burning sensation may be experienced for 5-10 minutes after application.
- Ulceration penetrating into the dermis may occur, and it is therefore not recommended for large volume warts.
- Trichloroacetic acid can be used at most anatomical sites.

Caution:

- Trichloroacetic acid is extremely corrosive to the skin. Careful application and protection of the surrounding skin with petroleum jelly is recommended. A neutralizing agent-for example, sodium bicarbonate, should always be available in case of excess application or spills.

5-Fluorouracil

5-Fluorouracil is a DNA antimetabolite, available in a 5% cream. Its use is limited by severe local side effects, which may result in long term problems- for example, neovascularisation and vulval burning. It may be teratogenic, therefore should not be used in pregnancy. It is not commonly used and as satisfactory alternatives exist, this treatment is no longer recommended unless with expert advice.

Interferons

Various regimens have been described using interferons alpha, beta, and gamma as creams and as intralesional or systemic injection (Ib, A).

- Its use is limited by expense, systemic side effects, and a variable response rate.
- Cyclical low dose injection used as an adjunct to laser therapy has resulted in a lower relapse rate. (Gross et al., 1996)
- Interferons should only be used on consultant advice.

Imiquimod

Imiquimod is an immune response modifier.

- Available as a 5% cream, it induces a cytokine response when applied to skin infected with human papilloma virus. (Slade et al., 1998)
- Suitable for use on all external anogenital warts, but is not recommended for use in pregnancy or internally.
- Use in uncircumcised men has been shown to be safe. (Gollnick et al., 2001)
- Cream is applied to lesions three times weekly and washed off 6-10 hours later for up to 16 weeks.
- Response to treatment may be delayed for some weeks.
- Clinical trials have shown response rates comparable with other chemical agents, but an encouragingly low relapse rate (Ib, A) (Edwards et al., 1998;

Beutner et al., 1998). An apparently low relapse rate has not been compared in clinical trials against other currently available therapies.

Caution: Not approved for use in pregnancy or internally.

Physical ablation

Excision (Ib, A)

- Removal of warts under local anaesthetic injection is particularly useful for pedunculated warts, and small numbers of keratinised ones at anatomically accessible sites.
- Haemostasis can be established using electrosurgery or application of a haemostatic solution.
- Treatment can be repeated as required. This is a good method of treatment for small numbers of warts and may be underused. (Bonnez et al., 1996)

Cryotherapy (Ib, A)

- Using a liquid nitrogen spray or a cryoprobe results in cytolysis at the dermal epidermal junction resulting in necrosis.
- Treatment should be applied until a "halo" of freezing has been established a few millimeters round the treated lesion.
- A freeze, thaw, freeze technique should be used

Electrosurgery (Ib, A)

Three types are commonly used:

- Electrocautery results in burning of the treatment site and surrounding tissue.
- Hyfrecator acts by electrofulgaration resulting in superficial charring and little dermal damage, or for deeper tissue penetration electro desiccation. These can be followed by curettage.
- Monopolar surgery- different waveforms can be generated, allowing desiccation, cutting, or coagulation. This results in a cleaner cut and less damage to surrounding tissue. (Gross & Barrasso, 1997)

Caution: leave skin bridges between treatment sites to aid healing and minimize scarring.

Laser treatment (IIa, B)

- The carbon dioxide laser is especially suitable for large volume warts and can be used at difficult anatomical sites, such as the urethral meatus, or intra-anal. (Ferenczy, 1984)

Caution: All electrosurgical and laser techniques result in a plume of smoke which has been shown to contain human papilloma virus deoxyribonucleic acid (DNA), which may potentially cause infection of the respiratory tract in operating personnel. Therefore, masks should be worn and adequate extraction provided during these procedures (IIb, B) (Ferenczy, Bergeron, & Richart, 1990).

Sexual partners

- Current sexual partner(s) may benefit from assessment as they may have undetected genital warts, undetected other sexually transmitted infections, or need an explanation and advice about disease process in partner (III, B).
- Tracing of previous sexual partner(s) is not recommended.

Follow-up

- Review at end of course to monitor response and assess need for changes in therapy. Patients whose original lesions have responded well to treatment but new lesions are evolving, can continue with current regimen.
- Change is indicated if (a) patient is not tolerating current treatment, (b) under 50% response to current treatment.
- Relapses should be treated as appropriate to the lesion types.

Special considerations

Anatomical sites

- Podophyllin and 5 Fluorouracil are no longer recommended for internal lesions

Intravaginal

- Cryotherapy, electrosurgery and trichloroacetic acid are recommended treatments.
- If Podophyllin is used it should be applied carefully to no more than a total area of 2 cm^2 weekly.

Cervix

- Best practice suggests colposcopy and biopsy before treatment decisions. (Murphy, Fairly, & Wilson, 1993)
- If no cervical intraepithelial neoplasia, cryotherapy, electrosurgery, or trichloroacetic acid may be used. If cervical intraepithelial neoplasia, refer for large loop excision of the transformation zone.

Urethral meatus

- If base of lesions seen, treatment with cryotherapy, electrosurgery, podophyllotoxin or imiquimod. Lesions deeper in the urethra should be referred to Urology for surgical ablation under direct vision.

Intra-anal

- Treatment options include trichloroacetic acid, cryotherapy, electrosurgery, and laser treatment.

Pregnancy

- Avoid podophyllin, podophyllotoxin, and 5-fluorouracil because of possible teratogenic effects.
- Imiquimod is not approved for use in pregnancy. If using after informed consent, treatment should be registered with 3M monitoring system
- Treatment aims to minimise the number of lesions present at delivery to reduce the neonatal exposure to virus.
- Potential problems for children are the development of laryngeal papillomatosis (Mounts, Shah, & Kashima, 1982) and anogenital warts. (Menton et al., 1993)
- Very rarely a caesarean section is indicated because of blockage of the vaginal outlet with warts or the presence of gross cervical warts.

Cervical cytology

- The National Health Service Cervical Screening Programme recommends that no changes are required to screening intervals in women with anogenital warts.
- Guidelines for the management of abnormal smears have been defined. (Duncan, 1997)

Immunosuppressed

- People with impaired cell mediated immunity- for example, renal transplant patients or human immunodeficiency virus (HIV) infection, are likely to have poor treatment responses, increased relapse rates, and dysplasia.
- Careful follow up is required in all these patients.

Definitions

The following rating scheme was used for major management recommendations.

Levels of Evidence

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of recommendations

A (Evidence levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.

B (Evidence levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.

C (Evidence level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
- Indicates absence of directly applicable studies of good quality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of genital warts for patients in the United Kingdom

- Improved wart clearance
- Decreased recurrence

POTENTIAL HARMS

Side effects of each treatment option are presented in the "Major Recommendations" field. Side effects may be minimized when the guideline user follows the cautions provided in the original guideline document.

CONTRAINDICATIONS

CONTRAINDICATIONS

Podophyllin, podophyllotoxin, and 5-fluororuracil are contraindicated in pregnancy because of possible teratogenic effects.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The Clinical Effectiveness Group reminds the reader that guidelines in themselves are of no use unless they are implemented systematically. The following auditable outcome measures are provided:

- Adherence to protocol, 90% of patients
- Percentage of patients with wart clearance at 3 months
- Percentage of patients with recurrence within 6 months of initial clearance

It is recommended that a continuing audit cycle be adopted to ensure effective use of a protocol and for the incorporation of any new treatments available.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline for the management of anogenital warts. London: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p. [43 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Aug (revised 2002)

GUIDELINE DEVELOPER(S)

British Association of Sexual Health and HIV - Medical Specialty Society

SOURCE(S) OF FUNDING

Not stated

GUIDELINE COMMITTEE

Clinical Effectiveness Group (CEG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Author: Raymond Maw

Human Papillomavirus (HPV) Special Interest Group of the Medical Society for the Study of Venereal Diseases (MSSVD): Humphrey Birley; Paul Fox; Richard Gilson; David Jenkins; Charles Lacey; Raymond Maw; Dilys Morgan; Jonathon Ross; David Rowen; Chris Sonnex

Clinical Effectiveness Group (CEG) Members: Keith Radcliffe (Chairman); Imtyaz Ahmed-Jushuf; Jan Welch; Mark FitzGerald; Janet Wilson

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr Birley has chaired a sponsored meeting for 3M; Dr Jenkins has acted as a consultant to Merck and 3M; Dr Maw has acted as a consultant to 3M, Perstorp and Stiefel; Dr Ross is in receipt of research grants from 3M and Stiefel; Dr Sonnex has conducted clinical trials for 3M and Stiefel

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates a previously released version.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in HTML format from the Association for Genitourinary Medicine (AGUM) Web site. Also available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- UK national guidelines on sexually transmitted infections and closely related conditions. Introduction. Sex Transm Infect 1999 Aug;75(Suppl 1):S2-3.

Electronic copies: Available in Portable Document Format (PDF) from the Medical Society for the Study of Venereal Diseases (MSSVD) Web site.

The following is also available:

- Revised UK national guidelines on sexually transmitted infections and closely related conditions 2002. Sex Transm Infect 2002;78:81-2

Print copies: For further information, please contact the journal publisher, BMJ Publishing Group.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 8, 2000. The information was verified by the guideline developer on January 12, 2001. This summary was updated on August 5, 2002.

COPYRIGHT STATEMENT

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